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ORIGINAL ARTICLE

Characteristics, outcome, and prognostic factors of young patients with central nervous system World Health Organization grade 3 oligodendrogliomas *IDH*-mutant and 1p/19q codeleted: A French POLA network study

Alexandre Bertucci MD[1,2] | Ondine Dufour MD[2] | Romain Appay MD, PhD[1,3] | Vincent Harlay MD[2] | François Ducray MD, PhD[4] | Charlotte Bronnimann MD[5] | Apolline Djelad MD[6] | Elisabeth Cohen-Jonathan Moyal MD, PhD[7] | Mario Campone MD[8] | Olivier Langlois MD[9] | Mathilde Ducloie MD[10] | Elodie Vauleon MD[11] | Nadia Younan MD[12] | Christine Desenclos MD[13] | Carole Ramirez MD[14] | Mehdi Touat MD, PhD[15] | Ahmed Idbaih MD[15] | Céline Bequet[2,16] | Dominique Figarella-Branger MD, PhD[1,16] | Caroline Dehais MD[15] | Olivier Chinot MD[1,2] | Emeline Tabouret MD, PhD[1,2,16] | for the POLA network

[1]Aix-Marseille Univ, CNRS, INP, Inst Neurophysiopathol, GlioME Team, Marseille, France

[2]APHM, CHU Timone, Service de Neurooncologie, Marseille, France

[3]APHM, CHU Timone, Service d'Anatomopathologie, Marseille, France

[4]Hospices Civils de Lyon, Hôpital Neurologique, Neuro-oncology Department, Department of Cancer Cell Plasticity, Cancer Research Center of Lyon, Claude Bernard University, Lyon, France

[5]Medical Oncology Department, CHU de Bordeaux, Bordeaux, France

[6]Neurosurgery Department, CHU de Lille, Lille, France

[7]Radiotherapy Department, IUCT-Oncopôle, Toulouse, France

[8]Medical Oncology Department, Centre René Gauducheau, Saint-Herblain, France

[9]Neurosurgery Department, CHU Charles Nicolle, Rouen, France

[10]Neurology Department, CHU Caen, Caen, France

[11]Centre Eugène Marquis, Medical Oncology, INSERM, University of Rennes, Rennes, France

[12]Neurology Department, Hôpital Foch, Suresnes, France

[13]Neurosurgery Department, Hôpital Nord, CHU Amiens, Amiens, France

[14]Neurology Department, Hôpital Nord, CHU Saint-Étienne, Saint-Priest en Jarez, France

[15]Sorbonne Université, Inserm, CNRS, UMR S 1127, Institut du Cerveau, ICM, AP-HP, Hôpitaux Universitaires La Pitié Salpêtrière-Charles Foix, Service de Neuro-oncologie, Paris, France

[16]Aix-Marseille Univ, Réseau Préclinique et Translationnel de Recherche en Neuro-oncologie, Plateforme PETRA"TECH" ou Plateforme PE"TRANSLA", Marseille, France

Correspondence
Emeline Tabouret, Neuro-Oncology Department, University Hospital La Timone, 264 rue Saint Pierre, 13005 Marseille, France.
Email: Emeline.tabouret@gmail.com

Funding information
French Institut National du Cancer

Abstract

Background: Brain tumors represent one of the main causes of cancer-related mortality in young patients. Among them, oligodendrogliomas (OG) are adult-type diffuse gliomas with the best prognosis. Nevertheless, characterization of these tumors in the young population remains poorly documented. Our objective was to characterize the population of young adults under 40 years of age with grade 3 OG in the POLA cohort.

Methods: Clinical data prospectively collected for all patients registered with grade 3 OG between April 2009 and August 2021 were extracted from the national POLA database. This study compared the patient subgroup <40 years of age to the one >40 years of age.

Results: The authors included 111 patients <40 years old and 363 patients ≥40 years old. Treatment received did not differ significantly between the two subgroups. Temporal location was more frequent in older patients ($p = .009$). Patients <40 years old presented more often seizure as initial symptom ($p = .003$). They had less frequent chromosome 9p loss ($p < .001$) and less *CDKN2A* homozygous deletion ($p = .024$). Median progression-free survival (PFS) was 123 months (range, 86–not reached [NR]) versus 88 months (range, 67–117) ($p = .082$) and median overall survival (OS) was not reached (range, 147–NR) versus 163 months (range, 137–NR) ($p < .001$) in younger and older subgroups, respectively. In multivariate analysis, complete or subtotal resection ($p = .014$) and seizure at diagnosis ($p = .032$) were associated with better OS.

Conclusion: Young patients with grade 3 OG have distinct clinical presentation, molecular features, and outcomes compared to the older patients.

KEYWORDS
glioma, grade 3 oligodendroglioma, molecular features, prognostic factors, young patient

INTRODUCTION

Global support and treatment of young patients with cancer is one of the major challenges of current oncology. Different publications suggest a distinct clinical, radiological, and biological presentation between young and older patients. These have notably been reported in lung and breast cancer.[1,2] In neuro-oncology, differences have also been suggested in epidemiology, histology, biology, survival rates, and overall treatment approaches between younger and older patients.[3–5] Given the lower incidence of cancer in young patients, they are often under-represented in clinical trials and their standards of care are not always well defined. Regarding post-cancer issues, the challenges encountered by the younger population (socio-professional reintegration) will be different than those of older patients and require dedicated management and follow-up.

Brain and central nervous system (CNS) tumors represent the first cause of mortality by cancer in occidental countries and the third worldwide (after leukemia and breast cancer) in the young population of patients under 40 years old (GLOBOCAN 2020). Adult-type diffuse gliomas are the most common primary malignant brain tumors. Among them, oligodendrogliomas (OGs) are associated with the best prognosis. From a molecular point of view, OG are characterized by 1p19q codeletion and mutation of the isocitrate dehydrogenase (*IDH*) 1 or 2 genes.[6] The survival of patients with OG has improved markedly over the last decades thanks to the combination of radiotherapy (RT) and chemotherapy (CT).[7] Clinical and molecular features of these young patients may differ from those of older patients.

This study aims to characterize the clinical presentation, molecular characteristics, therapeutic management, and survival of patients <40 years old with grade 3 OG (3OG) compared their older counterpart, from the prospective French national POLA cohort.

MATERIALS AND METHODS

Study design and data source

The POLA (Prise en charge des Oligodendrogliomes Anaplasiques) network is a national structure, labeled in 2009 by the French

National Cancer Institute, whose the aims are to provide a centralized pathological review and molecular analysis, to harmonize management, and to constitute a prospective database on high-grade de novo adult gliomas with an oligodendroglial component. From April 2009 to August 2021, 754 patients with World Health Organization (WHO) 3OG, *IDH*-mutant, and 1p/19q-codeleted, were included in the POLA cohort. All patients, except those included in the POLCA trial (NTC02444000), were included in the present study. A prospective record of medical, radiological, histological data, and treatment patterns was performed. The evaluation of surgical resection is performed by the neurosurgeon based on early postoperative imaging and intraoperative observations; a subtotal resection is defined as the removal of at least 90% of the enhanced tumor. In the POLA network, no centralized review is performed.

All patients were analyzed and segregated according to their age at diagnosis, with a threshold of 40 years defining the young population. We used the definition of the US National Cancer Institute for predetermining the threshold.[8,9]

The study was approved by a national ethics committee. Patients prospectively included into the POLA cohort provided their written consent for clinical data collection and molecular analysis according to national and POLA network policies.

Data collection

For all patients at diagnosis, we collected: clinical characteristics (sex, past medical post-surgery Karnofsky performance status [KPS]), symptoms (seizure, intracranial hypertension [based only on the presence of clinical symptoms], focal deficit, cognition, phasic, or memory impairment), radiological characteristics on magnetic resonance imaging (MRI), and treatment (surgery type and adjuvant treatment).

First-line treatment received after surgery were "wait and see," RT alone, CT alone, and RT in combination with CT. RT included conventional radiation therapy (60 Gy delivered in 30 fractions). RT with temozolomide (TMZ) was defined by Stupp protocol. First-line CT treatments included TMZ or procarbazine, CCNU, and vincristine (PCV) schedule. The tumor response and date of progression was assessed based on RANO criteria.[10]

Molecular analysis

Automated immunohistochemistry was performed on 4 μm-thick formalin-fixed paraffin-embedded (FFPE) sections with an avidin–biotin–peroxidase complex on Benchmark XT (Ventana Medical System Inc, Tucson, Arizona) using the Ventana Kit including DAB reagent to search for the expression of IDH1 R132H (Dianova, H09). When the immunostaining of the IDH1 R132H protein was negative or unreliable, the status of *IDH1* and *IDH2* mutation was assessed by direct sequencing using the Sanger method and primers, as described previously.[11]

Tumor DNA was extracted from frozen tissue, if available, or from FFPE samples using the iPrep ChargeSwitch Forensic Kit. Qualification and quantification of tumor DNA were performed using a NanoVue spectrophotometer and gel electrophoresis, respectively. The genomic profile and assessment of the 1p/19q codeletion status were determined as described previously.[12] When the available quantity was insufficient to perform single-nucleotide polymorphism or comparative genomic hybridization, microsatellite analysis was conducted instead. The 1p and 19q chromosomal regions were assessed using polymerase chain reaction techniques described elsewhere.[13,14] Results of molecular analyzes are extracted from the POLA electronic case report as previously reported.[15] The 9p deletion was defined by the loss of one or both short arms of chromosome 9. The *CDKN2A* gene deletion specifically referred to the homozygous loss of region 9p21.3, which corresponds to the location of the *CDKN2A* gene on the short arm of chromosome 9.

Statistical analysis

Patient and tumor characteristics are presented by standard descriptive statistics (mean, standard deviation, median and ranges for quantitative variables, and counts and frequency for categorical variables). To perform the receiver operating characteristic (ROC) analysis, we plotted the curve representing sensitivity against the false–positive rate at various thresholds, allowing us to determine the optimal age cutoff as a prognostic factor. For correlation analysis, continuous variables were compared using the Mann–Whitney *U* test. The χ^2 test (or Fisher exact test) was used to compare qualitative variables. Progression-free survival (PFS) was defined as the time from the date of surgery to recurrence or death from any cause, censored at the date of last contact. Overall survival (OS) was defined as the time from the date of surgery to death from any cause, censored at the date of last contact. Factors associated with PFS and OS were determined in univariate and multivariate analyses. PFS and OS were estimated using the Kaplan–Meier method and compared with the log-rank test. Cox proportional hazards models were used for multivariate analyses and for estimating hazard ratios in survival regression models. All statistical tests were two-sided, and the threshold for statistical significance was $p = .05$. Statistical analyses were performed using Graph Pad Prism V5.01 and on R software (version 4.3.1).

RESULTS

Patient characteristics

After exclusion of patients from the POLCA trial and exclusion of patients without a diagnosis of 3OG after molecular reclassification,[6] 474 patients with 3OG were included. At diagnosis, the median age was 49 (range, 19–87), and 7.7% of patients had a KPS <70. The main neurological symptoms at diagnosis were seizure (56.3%), intracranial

hypertension (29.1%), cognitive dysfunctions (15%), and focal deficits (11.2%). Complete resection was achieved in 27.8% of patients. As adjuvant treatment, patients were followed (wait and see), received RT only, CT only, Stupp protocol, or RT with PCV in 5.5%, 19.8%, 14.1%, 20.0%, and 36.9%, respectively (Table 1). Except for 1p/19q-codeletion, which by definition was present in all tumors, the most observed chromosome alterations were chromosome 9p loss (27.8%), gain of chromosome 7 (9.7%), and chromosome 10q loss (6.8%). *CDKN2A* homozygous deletions were present in 4.6%. Regarding mutations, the most observed alterations were *hTERT* gene mutation (93%), *FUBP1* gene mutation (27.7%), and *CIC* gene mutation (21.3%) (Table 2). A ROC analysis was performed to determine the optimal cutoff for the age as prognostic factor. The area under the curve was 0.681 (95% confidence interval [CI], 0.621–0.736; $p < .001$), and the optimal cutoff was 50.3 years old with 66.7% of sensitivity and 62.9% of specificity (Figure S1).

Comparison between young (40 years old) to the rest of population

Clinical and radiologic data

Among the 474 patients, 111 patients were younger than 40 years, and 363 patients were ≥40 years old at initial diagnosis (Table 1). Median age in the younger group was 34 years (range, 19–39) whereas median age in the older group was 54 years (range, 40–87). Seizure was more frequent at diagnosis in the younger group than in the older (70% in <40 vs. 53% in ≥40, $p = .003$). There was no significant difference between both groups for neuroimaging characteristics (necrosis, calcification, edema, mass effect, and contrast enhancement). Nevertheless, tumors were more frequently located in the temporal lobe in the older group (11% in <40 vs. 23% in ≥40, $p = .009$) (Figure 1). Regarding the surgical approaches, there was no significant difference in the younger group than in the older ($p = .089$). In the younger group (14% and 38%) and in the older group (23% and 39%) received Stupp protocol or RT with PCV, respectively.

Histological and molecular data

Histopathological characteristics, including atypia, necrosis, vascular proliferation, and calcification, were not significantly different between younger and older 3OG (Table 2). Regarding protein expression, glial fibrillary acidic protein (GFAP) and α-internexin (INA) expression differed between both subgroups, with GFAP expression positive in 71% of younger patients versus 80% of older patients ($p = .050$) and INA expression positive in 74% of younger patients versus 89% in older patients ($p < .001$). Finally, proliferation index did not differ between these two groups: Ki67-positive expression was ≥15% in 70% of younger patients versus 77% of older patients. Interestingly, molecular profiles were significantly different between younger and older 3OG patients. In the older group, patients presented with more frequent molecular alterations including more frequent *CDKN2A* homozygous deletions (1% in <40 vs. 7% in ≥40, $p = .024$) (Table 2). Concerning chromosome alterations, chromosome 9p loss (16% in <40 vs. 33% in ≥40, $p = .022$) was more frequent in the older subgroup. All feature differences between the two populations are summarized in Figure 2.

Survival

The median follow-up was 95 months for both groups. Median PFS was 123 months (95% CI, 86–NR) versus 88 months (95% CI, 67–117) ($p = .082$) and median OS was not reached (95% CI, 147–NR) versus 163 months (95% CI, 137–NR) ($p < .001$) for younger and older subgroups, respectively (Figure 3A,B). Regarding the young population (<40 years old) in univariate analysis, the presence of mass effect on MRI ($p = .006$) and the presence of a focal deficit ($p = .008$) (Figure S2) were associated with poor PFS. Absence of seizure ($p = .003$) (Figure S3), GFAP expression ($p = .043$), chromosome 9p loss ($p = .037$), pathological groups (defined in three groups: group 1, high mitotic count only; group 2, microvascular proliferation [MVP] and no necrosis; and group 3, MVP) ($p = .02$), and partial resection or biopsy ($p = .079$) (Figure S4) were associated with poor OS. In multivariate analysis, mass effect ($p = .022$) remained significantly associated with a poor PFS. Absence of seizure ($p = .026$) and partial resection or biopsy ($p = .038$) remained significantly associated with a poor OS. The prognostic factors observed in the young population are reported in Table 3. The prognostic factors observed in the older population were different than in the younger population. These are reported in Table S1. Finally, among younger patients, 19 died during the follow-up. The characteristics of these patients do not seem to reflect a specific pattern: in this group, seven patients had mass effect, seven patients had Ki67 >15%, six patients had chromosome 9p loss (including one patient with homozygous deletion of *CDKN2A*), and only two patients received PCV in first-line treatment (Table S2).

DISCUSSION

This study explored the specificities of young and older patients with 3OG to improve the characterization of the youngest population included in the POLA cohort. We observed significant differences in terms of clinical, histopathological, and molecular characteristics. To our knowledge, this study is the first analysis comparing these populations, with a specific focus on molecular profiles.

We showed that young patients had better OS than older patients. The results in terms of PFS were not significantly different; however, the curves showed a clear trend toward separation. Apart from a lack of progression events in this population, our hypothesis to explain these results is that recurrences are likely less aggressive in the younger population, notably due to a lower proportion of

TABLE 1 Characteristics of both cohorts (clinical, symptoms, radiology, and treatment).

	Total	Group <40 years old (*n* = 111)			Group ≥40 years old (*n* = 363)			
Characteristics	**No.**	**Total**	**No.**	**%**	**Total**	**No.**	**%**	***p***
Pathology								
Atypia	474	111			363			.990
No			49	44		160	44	
Yes			62	56		203	56	
Necrosis	421	111			310			.369
No			81	73		280	90	
Yes			30	27		30	10	
Vascular proliferation	473	111			362			.417
No			24	22		92	25	
Yes			87	78		270	75	
Calcification	470	110			360			.068
No			74	67		207	57	
Yes			36	33		153	43	
Immunohistochemistry								
GFAP expression	467	110			357			.050
No			32	29		72	20	
Yes			78	71		285	80	
OLIG2 expression	468	110			358			.435
No			0	0		2	1	
Yes			110	100		356	99	
INA expression	465	109			356			<.001
No			28	26		40	11	
Yes			81	74		316	89	
Ki67 <15%	473	111			362			.164
No			78	70		278	77	
Yes			33	30		84	23	
Molecular alterations								
CIC gene mutation	167	40			127			.239
No			19	47		47	37	
Yes			21	53		80	63	
FUBP1 gene mutation	119	28			91			.913
No			20	71		66	73	
Yes			8	29		25	27	
hTERT gene mutation	404	92			312			.805
No			6	7		22	7	
Yes			86	93		290	93	
CDKN2A homozygous deletion	399	99			300			.024
No			98	99		279	93	
Yes			1	1		21	7	

(Continues)

TABLE 1 (Continued)

Characteristics	Total No.	Group <40 years old (*n* = 111) Total	No.	%	Group ≥40 years old (*n* = 363) Total	No.	%	*p*
Chromosomic								
Chromosome 7 gain	456	107			349			.306
No			99	92		311	89	
Yes			8	8		38	11	
Chromosome 9p loss	458	108			350			<.001
No			93	86		233	67	
Yes			15	14		117	33	
Chromosome 10q loss	459	108			351			.820
No			101	93		326	93	
Yes			7	7		25	7	

Abbreviations: PCV, procarbazine + CCNU + vincristine; RT, radiotherapy; TMZ, temozolomide.

TABLE 2 Characteristics of both cohorts (pathology, molecular biology, and chromosomic alterations).

	PFS			OS		
	Univariate	Multivariate		Univariate	Multivariate	
Factors	*p*	*p*	HR (95% CI)	*p*	*p*	HR (95% CI)
Age, years	.471			.637		
Sex (women vs. men)	.207			.209		
KPS post-surgery (<70%)	.122			.15		
Seizure (yes vs. no)	.189	.141	0.57 (0.27–1.21)	.003	.032	0.32 (0.11–0.91)
Mass effect (yes vs. no)	.006	.022	4.20 (1.23–14.3)	.142		
Surgery (CR + STR vs. PR + B)	.147	.587	0.81 (0.38–1.72)	.079	.014	0.26 (0.09–0.76)
Radiation therapy (yes vs. no)	.915			.997		
Ki67 (cutoff: 15%)	.830			.602		
P53 expression (yes vs. no)	.433			.614		
GFAP expression (yes vs. no)	.444			.043	.143	1.01 (0.98–1.03)
Pathological groups	.113			.02	.085	2.01 (0.91–4.44)
Group 2	.587			.148		
Group 3	.135			.047	.121	5.69 (0.63–51.3)
INA expression (yes vs. no)	.570			.511		
Chromosome 7 gain (yes vs. no)	.462			.783		
Chromosome 9p loss (yes vs. no)	.699			.037	.27	1.91 (0.61–5.99)

Abbreviations: B, biopsy; CI, confidence interval; CR, complete resection; HR, hazard ratio; KPS, Karnofsky performance status; OS, overall survival; PFS, progression-free survival; PR, partial resection; STR, subtotal resection.

molecular or chromosomal abnormalities. In addition, the lack of central MRI review may have contributed to alter the strength of PFS measure.

Regarding the clinical presentation of the younger patients, 3OG were more frequently diagnosed after a seizure. Although our dataset did not include tumor size, we hypothesize that a smaller tumor in contact with the cortex could quickly trigger an initial seizure. This may facilitate an earlier diagnosis compared to nonspecific clinical symptoms such as headaches or cognitive impairments. It is also interesting to note that in our study, no specific neuroimaging pattern was associated with younger patients. Regarding the management between the two age subgroups, we observed that age does

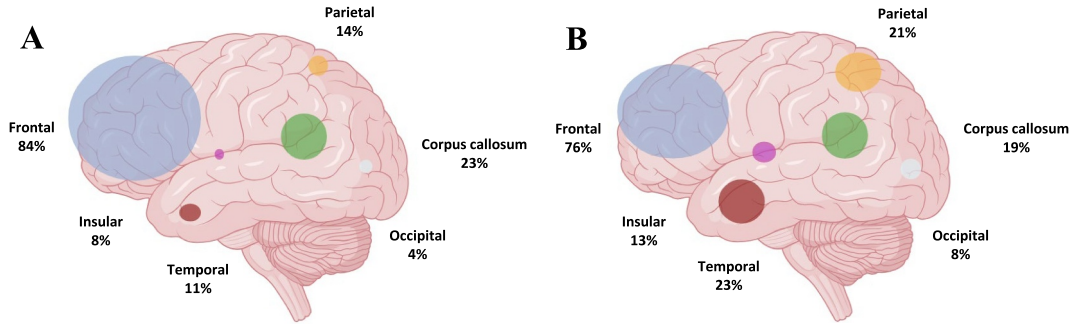

FIGURE 1 Distribution of tumor locations in (A) young adults <40 years old and (B) older patients ≥40 years old. Mann-Whitney *U* test for frontal lobe ($p = .076$), temporal lobe ($p = .009$), parietal lobe ($p = .114$), occipital lobe ($p = .133$), corpus callosum ($p = .392$), and insular lobe ($p = .136$).

not influence therapeutic decisions concerning adjuvant treatment, which is mostly represented by RT combined with TMZ or PCV. In the current study, we did not observe different regimen (RT-TMZ vs. RT-PCV) according to patient age. Nevertheless, in this population, Kacimi et al.[16] recently published the results of the difference between RT-PCV versus RT-TMZ, showing the superiority of RT-PCV. Therefore, all patients were able to receive treatment based on their clinical condition, without age limitation. In previous work,[17] we showed that even elder patients (>70 years old) could receive RT and CT with an acceptable safety profile.

The potential main result of this comparative analysis was the distinct molecular pattern of the disease in younger patients. First, we observed a more frequent occurrence of homozygous deletion of *CDKN2A* in the older patients. Among the 22 patients with this molecular alteration, only one was younger than 40 years old. In line with this observation, we also observed more frequent alterations of chromosome 9p in the older patients. The question rising from these observations is the rational of these distinct molecular patterns: are the younger diseases a distinct entity, with specific molecular profile and independent gliomagenesis, or are the differences reflecting the natural history of 3OG with cumulative incidence of molecular alteration and progressive enrichment leading to disease progression? In systemic oncology, previous publications reported distinctions between the same histological entities across different age classes.[18,19] In neuro-oncology, previous studies have reported differences between pediatric and adult OG patients.[20,21] In the larger cohort, the authors compared 346 pediatric (<25 years old) OG to 5753 adults OG. They found that tumor size, tumor grade, and RT were associated with overall survival for all patients. Additionally, they observed that pediatric patients less frequently had tumors in the frontal lobe and more frequently in the temporal lobe. These results differ from what we observed in the POLA population. However, it is important to notice that this first study did not evaluate the molecular profile of the tumor samples. In the second publication by Suri et al.,[20] the main result was based on the observation that pediatric OG rarely exhibited 1p/19q codeletion, which is now mandatory for diagnosis (even for younger patients), limiting the conclusions of this study. These last results and their limitations highlight the importance of diagnosis actualization based on the last WHO classification. Within the POLA cohort, all data were updated according to the 2021 WHO classification. Taken together, it is currently not possible to conclude if our observations revealed two distinct gliomagenesis or an historical continuum of molecular accumulations. The hypothesis of molecular continuum between 3OG diagnosed at an early age and those diagnosed after 40 years is supported by the difference in overall survival between younger and older patients, suggesting that older subjects present with more aggressive diseases potentially diagnosed at a later stage. However, the final answer will probably require complementary preclinical modeling and advanced omics analyses at the single-cell level to decipher the different OG trajectory evolutions. Nevertheless, a better characterization of tumors in adolescents and young adults is an important issue for current oncology, requiring specific clinical trials and cohorts (e.g., the EORTC SPECTA-AYA) that aims at characterizing high-grade gliomas and high-grade bone and soft tissue sarcomas at the European level.[22]

Our survival results confirm the data in the literature. In oncology, although 5-year relative survival of young patients compared to older is similar for all cancers combined, it varies according to the type of cancer with better survival for younger patients with gliomas and leukemias.[23] Similarly, younger patients of our cohort presented a better overall survival than older patients, with only 19 patients diagnosed before 40 years who had died at the time of the study. Regarding the specific prognostic factors in this young population, we validated the prognostic impact of seizure at diagnosis and complete or subtotal resection for OS, whereas mass effect at diagnosis on imaging was associated with worse PFS. The prognostic impact of seizure was already reported in some publications, including OG cohorts.[24] The positive impact of seizure as an initial symptom could be explained by the early diagnosis allowed by the occurrence of this symptom. Another interesting hypothesis is the potential anti-tumor effect of anti-seizure medications, particularly valproic acid, perampanel, and levetiracetam, whose possible therapeutic properties are currently being investigated.[25] The lack of data on anti-seizure medication in the POLA cohort does not allowed us to contribute more precisely to this question. We did not observe any impact of chromosomal alterations on survival. However, due to the small sample size, our study lacked sufficient

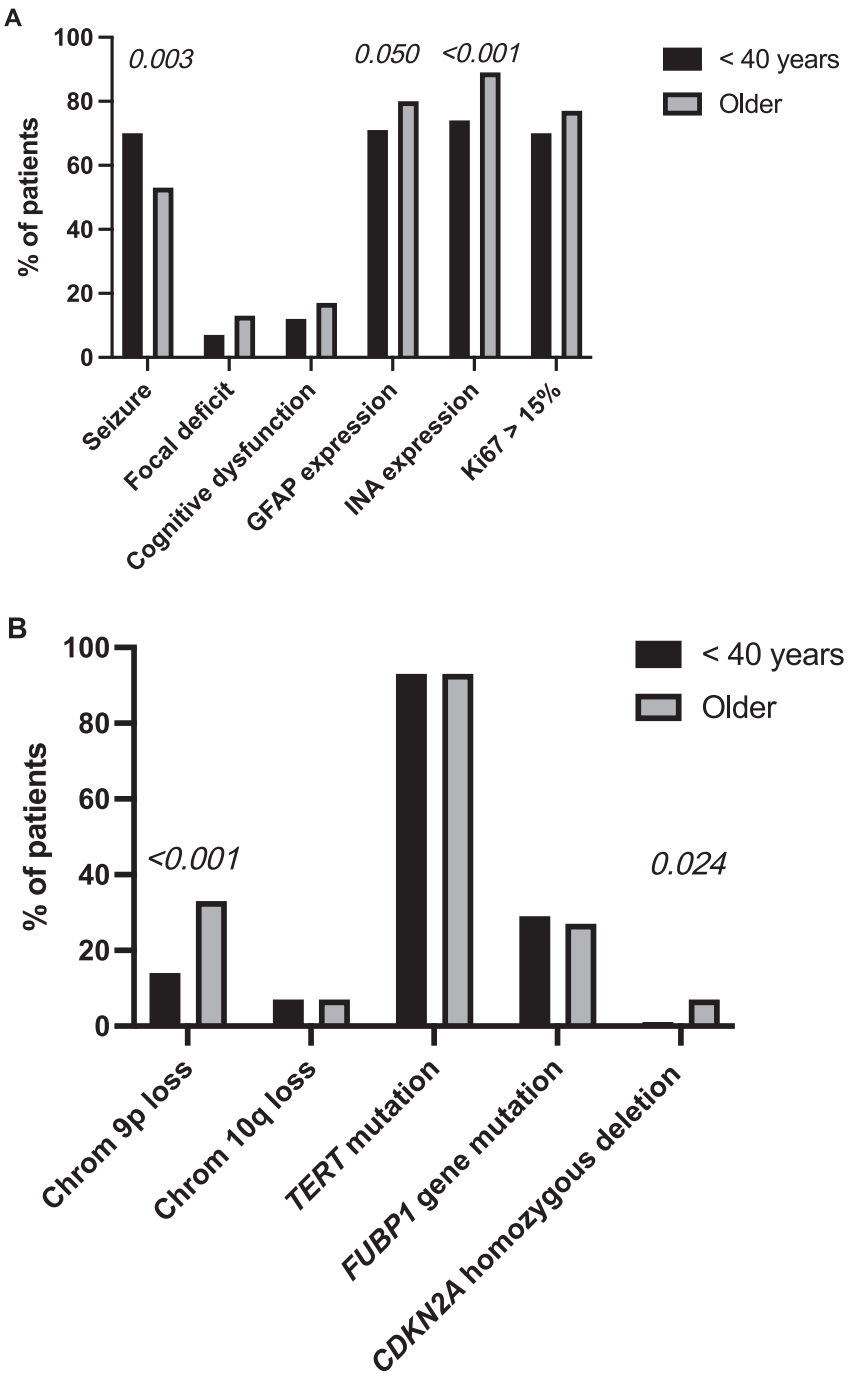

FIGURE 2 Impact of young age (<40 years) versus older age on clinical (A) and molecular (B) characteristics. Chrom indicates chromosome.

statistical power. The negative impact of *CDKN2A* homozygous deletion is now well established in recent literature[15] and has been incorporated into the latest WHO classification of CNS tumors for astrocytoma.[6] Concerning neurosurgical intervention, it is interesting to note that the complete or subtotal resection was associated with better OS but was not associated with better PFS. We could hypothesize that a complete or subtotal resection could lead to a smaller and less aggressive recurrence by limiting the remaining tumor cells. The initial prognostic impact of the 40-year-old age cutoff was published by Pignatti et al.[26] in 2002, before the identification of *IDH* mutations. These prognostic criteria are now debated. Moreover, the prognostic significance of age was recently evaluated in the whole POLA cohort of anaplastic oligodendroglioma by Figarella-Branger et al.,[27] and the cutoff of 50 years old was significantly correlated with both PFS and OS in this specific *IDH* I/2 mutated population.

Finally, comprehensive oncological care including notions of quality-of-life and social reinsertion after cancer treatment appears

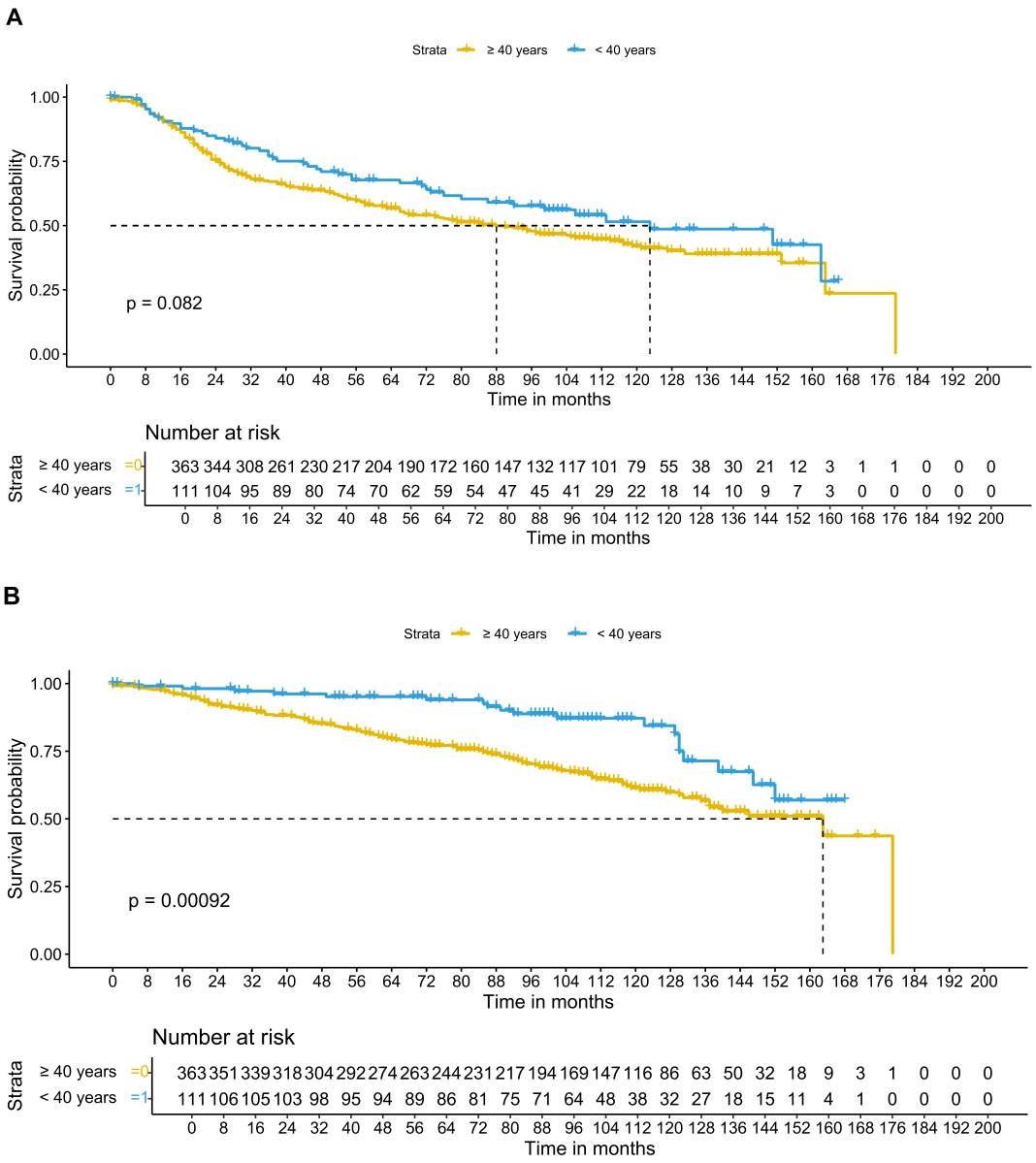

FIGURE 3 Progression-free survival (A) and overall survival (B) of patients according to their age subgroups.

essential, notably in the young population. The close follow-up of patients is too often limited to the period of active oncological treatment. Hence, this study also provides preliminary data allowing a precise definition of the young population of interest, supporting future qualitative prospective studies with systematic consideration of quality-of-life data for young patients with 3OG and, by extension, other brain tumors affecting young patients.

This work has several limitations. The main limitation is the absence of data on grade 2OG, which is directly related to the inclusion criteria of the POLA network dedicated to high-grade diffuse glioma with an oligodendroglial component. Data on grade 2OG would be interesting for understanding and validating its evolution over time, assuming that OG is a tumor that presents a continuum in its evolution from grade 2 to grade 3 (continuously acquiring molecular abnormalities over time leading to a more aggressive phenotype), and diagnosis is made sooner or later depending on location and symptoms. Another limitation is the absence of prospective characterization of seizure treatment during follow-up.[28] Nevertheless, this study is based on the largest prospective database dedicated to 3OG, the French POLA network, allowing us to provide a first comparative analysis of clinical, radiological and histomolecular characteristics in the young population.

In conclusion, young patients with 3OG have different clinical, biological, and molecular characteristics than their older counterparts, with less molecular abnormalities and better overall survival. These differences highlight and support the development of dedicated prospective studies for this young population, including specific programs following the oncological treatments.

TABLE 3 Prognostic factors for PFS and OS in the young patients <40 years old.

	Total	Group <40 years old (*n* = 111)			Group ≥40 years old (*n* = 363)			
Characteristics	**No.**	**Total**	**No.**	**%**	**Total**	**No.**	**%**	***p***
Clinical								
Sex	474	111			363			.844
Female			45	41		151	42	
Male			66	59		212	58	
Systemic medical history	445	99			346			<.001
No			57	58		121	35	
Yes			42	42		225	65	
Personal tumor history	446	98			348			<.001
No			91	93		270	78	
Yes			7	7		78	22	
Familial nervous system tumor history	360	72			288			.609
No			48	67		201	70	
Yes			24	33		87	30	
Karnofsky performance status	360	81			279			.142
≥70			78	96		255	91	
<70			3	4		24	9	
Symptoms								
Seizure	466	109			357			.003
No			33	30		166	47	
Yes			76	70		191	53	
Intracranial hypertension	463	109			354			.042
No			68	62		257	73	
Yes			41	38		97	27	
Focal deficit	462	108			354			.028
No			102	93		307	87	
Yes			6	7		47	13	
Cognitive symptom	459	108			351			.153
No			96	88		292	83	
Yes			12	12		59	17	
Neuroimaging								
Tumor location	469	109			360			.129
Median			6	5		13	4	
Left			44	40		161	45	
Right			54	50		157	43	
Bilateral			5	5		30	8	
Tumor multifocality	448	106			342			.461
No			98	92		308	90	
Yes			8	8		34	10	

TABLE 3 (Continued)

Characteristics	Total No.	Group <40 years old (n = 111) Total	No.	%	Group ≥40 years old (n = 363) Total	No.	%	p
Contrast enhancement	410	95			315			.658
No			30	32		92	29	
Yes			65	68		223	69	
Mass effect	304	70			234			.498
No			18	26		70	30	
Yes			52	74		164	70	
Necrosis	233	50			183			.751
No			38	76		135	74	
Yes			12	24		48	26	
Calcification	251	59			192			.416
No			30	51		86	45	
Yes			29	49		106	55	
Edema	275	63			213			.955
No			24	38		82	39	
Yes			39	62		131	61	
Treatments								
Surgery	449	101			348			.089
Biopsy			14	14		74	21	
Partial resection			25	25		89	26	
Subtotal resection			28	27		87	25	
Complete resection			34	34		98	28	
Post-surgical steroids	410	94			316			.419
No			47	50		143	45	
Yes			47	50		173	55	
Radiotherapy	460	104			356			.785
No			13	12		41	11	
Yes			91	88		315	89	
Adjuvant treatment	454	106			348			.795
Follow-up			7	6		19	5	
RT only			22	21		72	21	
RT + TMZ			15	14		79	23	
RT + PCV			40	38		136	39	
PCV only			13	12		29	8	
TMZ only			9	9		13	4	

Abbreviations: OS, overall survival; PCV, procarbazine, CCNU, and vincristine; PFS, progression-free survival; RT, radiotherapy; TMZ, temozolomide.

AUTHOR CONTRIBUTIONS

Alexandre Bertucci: Conceptualization, methodology, formal analysis, investigation, funding acquisition, and writing–original draft. **Ondine Dufour**: Conceptualization, funding acquisition, and writing–review and editing. **Romain Appay**: Writing–review and editing and validation. **Vincent Harlay**: Writing–review and editing. **François Ducray**: Writing–review and editing. **Charlotte Bronnimann**: Writing–review and editing. **Apolline Djelad**: Writing–review and

editing. **Elisabeth Cohen-Jonathan Moyal**: Writing–review and editing. **Mario Campone**: Writing–review and editing. **Olivier Langlois**: Writing–review and editing. **Mathilde Ducloie**: Writing–review and editing. **Elodie Vauleon**: Writing–review and editing. **Nadia Younan**: Writing–review and editing. **Christine Desenclos**: Writing–review and editing. **Carole Ramirez**: Writing–review and editing. **Mehdi Touat**: Writing–review and editing. **Ahmed Idbaih**: Writing–review and editing. **Céline Bequet**: Conceptualization and writing–review and editing. **Dominique Figarella-Branger**: Writing–review and editing and validation. **Caroline Dehais**: Project administration, data curation, resources, writing–review and editing, and validation. **Olivier Chinot**: Conceptualization, supervision, writing–review and editing, and validation. **Emeline Tabouret**: Conceptualization, supervision, methodology, project administration, writing–review and editing, writing–original draft, and validation.

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CONFLICT OF INTEREST STATEMENT

Mathilde Ducloie reports grant and/or contract funding from Novocure and Servier Azaires Medicales; and travel funding from Kyowa Hakko Kirin and Servier Pharmaceuticals LLC. Francois Ducray reports fees for professional activities from Novocure Israel Ltd; and consulting fees from Novocure Israel Ltd and Servier Azaires Medicales. Ondine Dufour reports travel funding from Roche. Ahmed Idbaih reports consulting fees from Boehringer Ingelheim, Leo Pharma, Novartis, Novocure, and Polytone Laser; grant and/or contract funding from Nutritheragene, Servier Pharmaceuticals LLC, and Transgene; and travel funding from Carthera, Leo Pharma, and Novocure Inc. Olivier Langlois reports fees for professional activities from Kyowa Kirin Pharmaceutical Development, Inc; and consulting fees from Seagen Inc and Servier Pharmaceuticals LLC. Emeline Tabouret reports consulting fees from Servier Pharmaceuticals LLC. Mehdi Touat reports consulting fees from NH Theraguix, Novocure, Ono Pharmaceuticals, and Servier Pharmaceuticals LLC. Elodie Vauleon reports fees for professional activities from Novocure and Servier Pharmaceuticals LLC. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Alexandre Bertucci https://orcid.org/0000-0002-9267-1770

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